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In the United States Patent and Trademark Office

In **Founds, et al.**

Serial No.: 09/465,444
Filing Date: December 16, 1999
For: **Monoclonal Antibodies Specific for Advanced Glycosylation Endproducts in Biological Samples**

Docket No.: 361331-009Re

Art Unit: 1644
Examiner: Nolan, P.

BOARD OF PATENT APPEALS AND INTERFERENCES

PATENT APPEAL

APPELLANT'S APPEAL BRIEF

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STATUTES

(1) Real Party in Interest

The inventors have assigned their interest to Alteon Inc. Accordingly, Alteon, Inc. ("Appellant") is the real party in interest.

(2) Related Appeals and Interferences

On information and belief, there are no other appeals or interferences that will directly affect or have a bearing on the Board's decision in this Appeal.

(3) Status of the Claims

Claims 1-9 and 11-16 are in the application. Claims 1-8 are the claims as originally issued in US Patent 5,698,197. All of the claims added in this reissue application are subject to rejections under 35 U.S.C. §103(a). Hence, claims 9 and 11-16 are appealed.

(4) Status of Amendments Filed After Final

The Amendment After Final submitted June 12, 2001 presented a minor amendment to claim 12, which the Office has entered. The pending claims are attached as Appendix A.

(5) Summary of Invention

By way of background, advanced glycosylation endproducts, or AGEs, are products from reactions of reducing sugars with biological molecules. AGE's and crosslinks resulting from certain AGEs have been implicated in stiffening and loss of function in tissues, organs and vessels, often associated with diabetes. A recently reported Phase IIa clinical trial on a compound developed by Alteon that *in vitro* breaks AGE-mediated crosslinks shows a statistically significant reduction in the arterial pulse pressure, defined by the difference between systolic and diastolic blood pressures. PR Newswire, January 3, 2001. Dow Jones Newswires, January 3, 2001.

In seeking to bring to issue the application that matured to US Patent 5,698,197, the claims of which focused on antibody 4G9, Appellant provided proof that that antibody was substantially superior to the relevant monoclonal antibody in the art. The patent specification expressly supported an invention to antibodies with a binding characteristic of antibody 4G9. In this reissue application, Appellant seeks claims of the scope to which it had a right. Thus, claim 9 reads:

> 9. A monoclonal antibody, or an antigen binding fragment thereof reactive with in vivo produced advanced glycosylation endproducts (AGEs), wherein the antibody or fragment is selected such that antigen binding measured by binding competition by 6-aminocaproic acid browned with glucose matches that of
>
> > a reference binding moiety which is monoclonal antibody 4G9 produced by hybridoma 4G9, deposited with the American Type Culture Collection (ATCC) and assigned Accession Number CRL 11626 or a fragment thereof corresponding to the antigen binding fragment.

(6) Issues

The issue before the board is whether the claimed monoclonal antibodies, having the high affinity for a certain type of AGE set forth in the comparative standard recited in the claim, would have been obvious under 35 U.S.C. §103 in view of two articles on polyclonal antibodies that bind AGEs and a compilation of antibody protocols. In one aspect, the issue is whether there was motivation in the art to use the affinity standard recited in the claim to optimize the prior art. In another aspect, the issue is whether the Office has relied on an improper "obvious to try" standard. Perhaps most tellingly, the issue is whether one would have a reasonable expectation of obtaining the claimed monoclonal antibodies that are in excess of two orders of magnitude better than the antibodies of the most germane prior art teachings in this record.

(7) Grouping of claims

The issue on appeal can be decided with respect to claim 9. Thus, the claims can be grouped together with respect to the issue on appeal.

(8) Argument

Claims 9, 11 and 13-16 stand rejected under 35 U.S.C. §103(a), based primarily on Makita, as represented by one or both of a 1992 J. Biol. Chem. article (Makita-1, Exhibit E1) or a 1992 Science article (Makita-2, Exhibit E2), in view of Harlow, Antibodies: A Laboratory Manual, Cold Spring Harbor Press, 1988 (Exhibit E3, a compilation of antibody protocols). Claim 12 stands rejected under 35 U.S.C. 103(a) based on the above documents in further combination with a document having disclosure on humanized antibodies.

The discussion below will show that there was no basis in the art to select 6-aminocaproic acid browned with glucose as the binding standard against which to measure binding of hybridoma clones and optimize a clone selection that might produce relevant monoclonal antibodies. Further, the Office has provided support for at most a supposition that it was "obvious to try" to make monoclonal antibodies, and "obvious to try" does not support a rejection under 35 U.S.C. 103. Moreover, assuming one sought to make monoclonal antibodies, after fortuitously selecting the binding standard relevant to obtaining appropriately optimized antibodies, one would not have had a reasonable expectation of success in obtaining antibodies that art in excess of two orders of magnitude better than the most germane antibodies in this record.

Makita-1, J. Biol. Chem. 267: 5133, 1992, is about immunochemical detection of AGEs with a polyclonal antibody. The antibody is made with AGE-RNase, which is made by "incubating RNase (25 mg/ml) with 0.5 M glucose in 0.2 M $NaPO_4$ buffer (pH 7.4) for 21 days." Exhibit E1 at 5134, column 1. Rabbits "received four primary and one booster immunization of RNase or AGE-RNase emulsified in Freund's complete adjuvant..." Exhibit E1 at 5134, column 2. Appellant's initial immunization was of mice injected with AGE-keyhole limpet hemocyanin. However, the important distinction is that Appellant's selected a specific clone from a hybridoma selection process initiated with B-cells from the immunized mice.

Makita-2, Science 258: 651, 1992, refers to Makita-1 as describing the antibodies. Hence, Makita-2 is cumulative, and the most relevant document is Makita-1.

Harlow is a basic manual of procedures for making monoclonal antibodies.

The Examiner's position is that one would have been motivated to make monoclonal antibodies and to seek antibodies of sufficient affinity that they would have met the affinity standard set forth in the claims. Particularly, the Office action dated May 31, 2000 asserted:

> Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to be motivated to generate hybridomas and monoclonal antibodies given the teachings of Makita et al., Makita et al. and Harlow et al. because Harlow et al. teach that hybridomas produce monoclonal antibodies that have homogeneous specificity and affinity for antigen thereby providing an expectation of success...[in meeting the claim requirements for affinity] since monoclonal antibodies that bind with high specificity are art recognized to be desirable since less antibody is required to perform an assay.

As implied by the above summary, no monoclonal antibodies specific for AGEs are described in the cited art. The suggestion by the Examiner that high affinity is desirable can be accepted as accurate. However, nothing in the cited art indicates that one should select, as the measure of high affinity, binding of 6-aminocaproic acid browned with glucose. It may be that the Examiner is under the misapprehension that there is but one standard for AGE binding, or that the measures of AGE binding are fully substitutable. However, AGEs arise in a variety of forms, giving rise to no universal surrogate chemical moiety. This is indicated in Appellant's specification by the differing affinities obtained against different standards. See, Col. 15, Table 1.

To determine obviousness, four factual inquiries must be made concerning: 1) the scope and content of the prior art; 2) the level of ordinary skill in the art; 3) the differences between the claimed invention and the prior art; and 4) secondary considerations of nonobviousness, which in case law is often said to include commercial success, long-felt but unresolved need, failure of others, copying, and unexpected results. Graham v. John Deere Co., 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966); Ruiz v. A.B. Chance Co. 234 F.3d 654, 662, 57 USPQ2d 1161, 1165 (Fed. Cir. 2000) (attached as Exhibit E4). To prevent a hindsight-based

obviousness analysis, the Court of Appeals for the Federal Circuit has "clearly established that the relevant inquiry for determining the scope and content of the prior art is whether there is a *reason, suggestion, or motivation* in the prior art or elsewhere that would have led one of ordinary skill in the art to combine the references." Ruiz at 664, 57 USPQ2d at 1167 (emphasis added).

Thus, a properly framed rejection under 35 U.S.C. §103 must take into account Appellant's selection of the 6-aminocaproic acid browned with glucose standard as a difference between the claimed invention and the cited art, and provide a *motivation* for making this change in the art. The Office Actions have provided no such support for the rejection. Accordingly, for this first reason, the rejection should be withdrawn. That selecting 6-aminocaproic acid browned with glucose as the comparative standard is not equivalent to other AGE standards is further illustrated in the data presented in the Declaration of Dr. Henry Founds (the "Founds Declaration," copy attached as Exhibit E5).[1] That data shows that while Appellant's monoclonal antibody is in excess of two orders of magnitude better than a prior art monoclonal as measured using the recited aminocaproic acid standard, it is only on the order of 14 times better with respect to β-Ala-Glu browned with glucose.

It is not sufficient to support legal obviousness that it was "obvious to try" a modification of the prior art. The Court of Appeals for the Federal Circuit has explained that an "'Obvious to try' situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued. In re Lilly & Co., 902 F.2d 943,

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[1] The Office action dated March 12, 2001 asserted that "the declaration filed in the Parent case has [not] been received for consideration in the present case." Appellant respectfully submits that there is no statutory basis to conclude that a Declaration of an inventor, having the declaratory representations required by 37 CFR §1.68, meeting the signature requirements of 37 CFR §1.4, and timely submitted for its evidentiary weight (prior to any final Office Action), has not been received for consideration. Accordingly, Appellant submits to the contrary that the Declaration is properly in this record.

945, 14 USPQ2d 1741, 1743 (Fed. Cir. 1990) (attached as Exhibit E6). Thus, in one case, while it was obvious to try to use a carbon-catalyzed reaction with hydrazine to deoxygenate a liquid in light of an old scientific paper, it was not obvious it could be reduced to the commercially effective claimed process. Ecolochem, Inc. v. Southern California Edison Co. 227 F.3d 1361, 1374-5, 56 USPQ2d 1065, 1075-6 (Fed. Cir. 2000) (attached as Exhibit E7).

Thus, it cannot simply be "obvious" that high affinity antibodies should be sought, it must be obvious at the time of the invention that antibodies with the required affinity, those which match antibodies from hybridoma 4G9, can be made. Appellants provided powerful evidence to the contrary in the Declaration of Dr. Henry Founds.

The evidence presented in the Founds Declaration showed a comparison to closer prior art than that cited in the present rejection. The art cited in the present rejection has no monoclonal antibodies against which to make a comparison. Thus, if comparative evidence is to show an objective basis to question the rejection, it must come from other art, which conveniently is also more relevant art. This more relevant art, Horiuchi, J. Biol. Chem. 266: 7329-7332, 1991, teaches a monoclonal antibody that recognizes AGE-modified ε-amino-caproic acid. (The Horiuchi article attached as Exhibit E8.) Thus, looking at the closest art, the monoclonal antibodies reported in that art have in excess of two orders of magnitude less affinity than required by the present claims. These prior art antibodies were the basis of at least the cited report in one of the premier journals in Biochemistry, the Journal of Biological Chemistry, and a second report in the same journal. In the second report, Araki et al., J. Biol. Chem. 267: 10211-10214, 1992, the antibody was used to measure the presence of AGEs in human lens protein, and to make a correlation with age. (The Araki article attached as Exhibit E9.) Appellant would respectfully submit that nothing in these premium, peer-reviewed articles would suggest to one of ordinary skill that antibodies with such remarkably higher affinity as those now claimed could or should be obtained.

Moreover, the test is whether one of ordinary skill would recognize that such high affinity antibodies could be obtained with a reasonable expectation of success. In Life Technologies v. Clontech Laboratories, the Federal Circuit found an "impermissible use of hindsight" in a trial court finding of obviousness (made in the context of an inequitable conduct

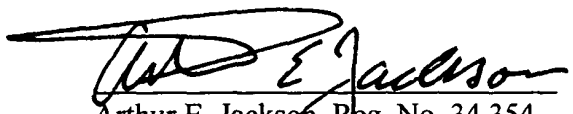
finding). The trial court finding was that the molecular biology deletions needed to make reverse transcriptase lacking RNase H activity were obvious in view of a bioinformatics-based article that predicted correctly the sequence responsible for RNase H activity. Life Technologies, 224 F.3d 1320, 1326, 56 USPQ2d 1186, 1190-91 (Fed. Cir. 2000) (attached as Exhibit E10). The reason for this holding was the lack of a reasonable expectation of success, which is assessed without reference to the inventor's success. Id. In the same way, without Appellants' results as guidance, one of ordinary skill would not suppose, with a reasonable expectation of success, that one could obtain monoclonal antibodies with in excess of two orders of magnitude more affinity than those of Horiuchi.

In view of the above discussion, it is submitted that a person of ordinary skill having before him or her either the cited art or the more relevant Horiuchi report would have no motivation to modify the art by selecting 6-aminocaproic acid browned with glucose as the binding standard for optimizing clone selection such that one might produce relevant monoclonal antibodies. A person of ordinary skill having before him or her this art might have his or her interest piqued to motivate investigation, but this "obvious to try" circumstance does not support statutory obviousness. Clearly, a person of ordinary skill having before him or her this art could not have a reasonable expectation of achieving monoclonal antibodies that are in excess of two orders of magnitude better than monoclonal antibodies effective to support two scientific articles in a premium, peer-reviewed, scientific journal.

Accordingly, the asserted obviousness flows from improper reliance on Appellants' own finding that such antibodies are obtainable. Thus, Appellant submits that the rejection must be withdrawn.

CONCLUSION

For the foregoing reasons, Appellant respectfully requests that the rejections under 35 U.S.C. §103(a) with respect to all o claims 9 and 11-16, be reversed and the pending claims in the application allowed.



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